IDIOPATHIC HYPERLIPEMIC AND PRIMARY HYPERCHOLESTEREMIC XANTHOMATOSIS*

I. Clinical Data and Analysis of the Plasma Lipids

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Two diseases are recognized in which there is a great increase in plasma cholesterol and phospholipids for no apparent reason: primary hypercholesteremic xanthomatosis and idiopathic hyperlipemia. They differ in that only the latter shows an increase in the amount of neutral fat in the plasma, giving the plasma a milky appearance, while the plasma in primary hypercholesteremic xanthomatosis is clear. Inspection of the plasma obtained in the fasting state thus provides a simple means of differentiation between the two diseases, which may resemble each other in their clinical manifestations since both may show tuberous xanthomata of the skin as well as tendon xanthomata.

It is the purpose of this communication to report the clinical and chemical findings in 7 patients with idiopathic hyperlipemia—all but 2 of whom showed tuberous xanthomata of the skin—and to compare these findings with those in 10 patients with primary hypercholesteremic xanthomatosis.

REVIEW OF LITERATURE

1. Idiopathic Hyperlipemia. The term hyperlipemia signifies an increase in the amount of neutral fat in the blood serum that is sufficiently large to cause turbidity of the serum. There are three types of hyperlipemia: alimentary hyperlipemia, secondary hyperlipemia and idiopathic hyperlipemia. Alimentary hyperlipemia physiologically follows the ingestion of a fat-rich meal and reaches a maximum after four to six hours. There is no significant increase in cholesterol or phospholipids. Secondary hyperlipemia may occur secondarily to severe diabetes, in the nephrotic stage of glomerulonephritis, and in von Gierke's disease. In addition, it has been considered by some to occur secondary to recurrent pancreatitis; but it is more likely, as will be discussed later, that recurrent pancreatitis is not a cause of hyperlipemia but may be a manifestation of idiopathic hyperlipemia. The third form of hyperlipemia, idiopathic hyperlipemia, represents a condition in which hyperlipemia is present without apparent cause. In both secondary and idiopathic hyperlipemia the amounts of cholesterol and phospholipids are increased as well as that of neutral fat. Cutaneous xanthomata may occur in both.

Forty-one cases of idiopathic hyperlipemia were found in the literature and their main features are recorded in Table 1 (1–32). Whether or not the hyperlipemia is always present at birth or may develop later in life cannot be ascertained from the reported cases, but in 15 patients the existence of the disease was established prior to ten years of age and in over two-thirds of the patients the disease was present before the age of 30. One or more members of the patient's family were found to have lipemic serum in 7 cases (11, 14, 18, 21, 28, 31, 32).

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TABLE 1

Essential data concerning the 41 patients with idiopathic hyperlipemia reported in the literature

NUMBER OF REFERENCE	SEX	FAMILIAL OCCURRENCE	AGE AT ONSET	FIRST SYMPTOM	ERUPTIVE XANTHOMAS		ENLARGEMENT OF			ABDOM. PAIN + PANCREATITIS ++	AMYLASE INCREASED	GLYCOSURIA	HYPERGLYCEMIA	SED. RATE	SPONTAN. DECREASE OF PLASMA LIPIDS	DECREASE OF PLASMA LIPIDS ON DIET	TOTAL LIPIDS	NEUTRAL FAT	PHOSPHOLIPIDS	CHOLESTEROL	
					(M = mouth)	Improved on diet	liver	spleen	liver/spleen decreased on diet					mm./hr.						Total	Esterified
																	mg./100 ml. serum				%
1	M		26	Xanth.	+	+				++		+								860	
2	M		22	Abd. pain	−		−			+		−	−				8110			760	
3	M	−	<1	Xanth.	+M	+	+	+	+	−		−	−	20		+	9476		1740	686	55
4	M		35	Abd. pain	−		−	−		+	+	+	+	32	+		4480			1040	48
5	M		5	Abd. pain	−		−	+		+		−	−	18			2226		1006	451	27
6	M	−	27	Abd. pain	−		+	−		+			−	4		+				321	
7	F		11	Turbid ser.	+	−	−	+	+	−		−	−			+	5180		400	300	30
8	F	−	<1	Splenomeg.	−		−	+		−		−	−				3540			188	
9	F		16	Abd. pain	−					++	+				+					360	
	F		34	Abd. pain	−					++					+					299	
	M		43	Xanth.	+					++					+					500	
	M		36	Abd. pain	−					+					+					436	
10	M		2	Xanth.	+	+	+	+	+	−		−	−			+	7430	5430	941	1059	64
11	F	+	4	Abd. pain	−		+	+	+	+	−	−	−	23	+	+	8200		453	398	61
12	M	−	1	Turbid ser.	+M	+	+	+	+	−	−	−	−			+	3954	2172	465	379	58
13	M		6	Abd. pain	−		+	+	+	+		−	−			+	9370	7636	833	901	78
14	M	+	8	Abd. pain	−		+	+	+	+		−	−			+				329	
15	M		27	Xanth.	+		−	−		+	−	−	−			+				864	
16	M	−	27	Abd. pain	−		+	+		+	−	−	−			+	4750		288	500	
17	M		4	Abd. pain	+	+	+	+		++	+	+	−	63	+	+					
18	M	+	16	Turbid ser.	−		+	+	+	−	−	−	−	45		+	9935	7767	1200	968	59
19	M	−	24	Abd. pain	−		+	+		+	−	−	−			+		3202	328	250	40
20	M	−	52	Abd. pain	−		+	−	+	+	−	−				+		3440	188	555	57
21	F	+	5	Abd. pain	−		+			++	+		−	16			4210	3565	241	320	58
	M	+	4	Abd. pain	−		+	+		+	+		−	40			12400			762	54
22	M		46	Xanth.	+	+	+	+		−		+	+	22		+		4477	810	693	53
	M		26	Turbid ser.	+		−	−		−		−	−	16				3632	657	486	44
	M		22	Xanth.	−		+	−		−		−				+		3202	328	250	40
	M		34	Turbid ser.	+	+				−		+	+	24				6570	400	900	55
23	M		2	Hepatomeg.	+	+	+	+	+	+	−	−	−			+	2700		424	287	43
24	F		<1	Turbid ser.	+		−	−		−		−	−				6252	4650	592	740	55
25	M		35	Xanth.	+M	+				−			−			+	2164			974	
26	F		6	Abd. pain			−	−		+		−	−				6500	5174	494	450	67
27	M		28	Xanth.	+		−	−		−		−	−				1880		400	1409	58
28	M	+	23	Turbid ser.	−		+	+		−		−	−				4540			130	
29	M	−	42	Turbid ser.	−		+	−	+	−	−	−	−				9320		1100	832	59
	M	−	8	Abd. pain	−		+	+		+	−		−				3300		500	197	72
	M		48	Hepatomeg.	−		+	+	+	−			−			+	3060		428	144	68
30	M		47	Xanth.	+	+	−	−	−	−						+	3500			736	65
31	M	+	42	Xanth.	+	+	+	−	−	−		−				+	2560		840	310	51
32	M	+	18	Xanth.	+	+	−	−		++	+	−	−			+	1941	1302	364	275	63

It is impossible, however, to estimate how common the familial incidence is because in many reported cases there is no record of the state of the relatives' serum. The cause of idiopathic hyperlipemia is not definitely known, but it is likely that defective removal of fat from the blood is an important factor. This is suggested by the studies of Thannhauser and Stanley (33) who administered by mouth iodine^{131}-labelled neutral fat to normal subjects and to those with idiopathic hyperlipemia. They found that the disappearance of iodine from the blood serum was considerably prolonged in the latter as compared with the normal subjects. The theory of delayed removal of lipid from the blood would explain why the patients with this disorder, in contrast to those with primary familial xanthomatosis, improve considerably when placed on a diet low in fat.

Cutaneous xanthomata were present in 18 of the 41 patients reported in the literature (see Table 1). The xanthomata consisted of soft, yellowish papules and nodules most commonly located on the extensor aspects of the knees and elbows, on the buttocks and thighs, but also on the trunk, face, hands and feet. Occasionally, lesions were noted on the buccal mucous membrane (cases 3, 12, 25). Although in one patient (12) a few papular xanthomata were present along the free edge of the eyelids ("resembling chalazia") none had xanthelasmata on the eyelids. The lesions, as a rule, measured only a few millimeters in diameter. On the elbows and knees, however, their size was occasionally larger, "as large as a pea" (22). Many authors (1, 3, 10, 12, 17, 22, 23, 25, 30, 31, 32) have observed that the xanthomata decreased in size and number, and even disappeared when dietary fat was restricted. Because of their ephemeral nature they have been called eruptive xanthomata. Apparently there is no critical level for either neutral fat or cholesterol at which the xanthomatous lesions appear. One patient (18) with a neutral fat level of 7,767 mg. and a cholesterol level of 968 mg. per 100 ml. of plasma had no xanthomata, while another patient (32) in whom the concentration of neutral fat was 1,302 mg. per 100 ml. and that of cholesterol 275 mg. had typical lesions. None of the accounts mention the presence of tendon xanthomata, but only one (32) specifically notes their absence.

Attacks of upper abdominal pain occurred in 23 of the 41 patients (see Table 1). That pancreatitis can be the cause of the abdominal colics occurring in idiopathic hyperlipemia has been adequately proved in 9 cases, either by exploratory operation (cases 1, 9a–c, 17, 21a, 32) or by raised levels of amylase in the serum or urine (cases 4, 9a, 17, 21a & b, 32), and it is likely that in most of the other cases pancreatitis was also the cause of the colics. Klatskin and Gordon (32) state as an argument in favor of this view that it is often most difficult to prove the presence of pancreatitis except by exploratory operation since amylase levels in pancreatitis may be abnormally high for only a short period at the onset of the disease. They admit, however, that in some instances, such as in Holt's case (12), where periodic swelling of the liver occurred with each abdominal attack, the abdominal pain may have been caused by distension of the liver. Their theory is that emboli of agglutinated serum lipid particles in the pancreas and liver produce the abdominal crises.

There still is no unanimity as to whether the pancreatitis always follows the hyperlipemia; or whether the pancreatitis may be the primary condition and give rise to hyperlipemia. As a matter of fact, several cases included in this survey were reported not as idiopathic hyperlipemia but as instances of pancreatitis with secondary hyperlipemia (cases 1, 4, 6, 9a–d, 17). Among recent investigators, Thannhauser (22) still regards hyperlipemia in chronic pancreatitis as a disease entity and different from idiopathic hyperlipemia with abdominal colics. He believes that chronic pancreatitis can cause hyperlipemia and that in the patients reported merely as having abdominal colics there was not sufficient evidence for the existence of pancreatitis. Klatskin and Gordon (32), however, enumerate the following points in favor of the view that pancreatitis is secondary to the hyperlipemia rather than its cause: first, 4 patients (cases 1, 15, 17, 32) had cutaneous xanthomata before attacks of abdominal pain began to occur; second, one patient (case 21b) still had hyperlipemia eight years after the last episode of pain; and third, in 3 patients with pancreatitis and hyperlipemia (cases 11, 14, 32) other members of their families had asymptomatic hyperlipemia.

The liver was reported as enlarged in 22 cases and as normal in size in 12, while the spleen

was found to be large in 19 cases and not palpable in 13. In one instance (case 11) these organs increased in size with each attack of abdominal pain, and spontaneously decreased after the attacks. In many patients, (cases 3, 7, 10, 11, 12, 13, 14, 18, 20, 23, 29 a & c) a diet low in fat resulted in a decrease in size of the enlarged liver and spleen.

Glycosuria and hyperglycemia were occasionally present, but since they could be controlled in some cases by restricting the intake of fat, Thannhauser (22) has expressed the view that they were not manifestations of diabetes.

The existence of cardio-vascular disease has not been recorded in any of the cases reported in the literature.

All reported cases of hyperlipemia had abnormally high levels of total lipids in the serum, varying from 1,880 to 12,400 mg. per 100 ml., as compared to a normal range of 400 to 700 mg. The excess in total lipids was accounted for largely by an increase in neutral fat which varied from 1,302 to 7,767 mg. per 100 ml., whereas the normal range of values extends from 0 to 400 mg. The concentrations of cholesterol and phospholipids were also increased, but to a lesser degree. Nevertheless, in 3 patients the cholesterol measured over 1,000 mg. per 100 ml. of serum, and in 4 others the phospholipid level was over 1,000 mg.

The values for neutral fat, cholesterol and phospholipids often fluctuated and in several patients decreased spontaneously; and on a diet low in fat they frequently fell considerably but hardly ever to normal amounts (see Table 1).

2. Primary Hypercholesteremic Xanthomatosis. Individual accounts of primary hypercholesteremic xanthomatosis will not be reviewed since this condition is much better known than idiopathic hyperlipemia and the state of present knowledge is well summarized by Thannhauser (22) and by Froehlich (26). The main points of differentiation from idiopathic hyperlipemia, as presented in the literature, are: First, the fasting serum is always clear. Second, the xanthomata differ in location and size from those present in idiopathic hyperlipemia. They are frequently present as flat xanthelasmata on the eyelids, where lesions have so far never been observed in idiopathic hyperlipemia, and as large tuberous xanthomata. The latter, present particularly over the elbows and knees, are stated to be larger than the papular xanthomata of idiopathic hyperlipemia and not to vary in size either spontaneously or as a result of dietary restrictions. Third, tendon involvement is frequently seen, particularly of the Achilles tendons, the extensor tendons of the hands and the patellar tendons. Fourth, early atherosclerotic cardiovascular disease is common, leading to death from coronary occlusion in early adult life in a significant number of patients. Fifth, a familial incidence is more commonly reported in this disease than in idiopathic hyperlipemia. In affected families hypercholesteremia may occur as the only abnormality in some members, representing a *forme fruste* of the disease, while in other members clinical manifestations are present in addition to the hypercholesteremia. It should be remembered that xanthelasmata of the eyelids are not necessarily evidence of primary hypercholesteremic xanthomatosis since they may occur in otherwise normal individuals (34).

Analysis of the fasting serum in primary hypercholesteremic xanthomatosis reveals a normal amount of neutral fat but an elevation of the amounts of cholesterol and phospholipids.

A. Clinical Data

1. Idiopathic Hyperlipemia. Seven patients with idiopathic hyperlipemia were studied (Table 2). All but 1 patient (case 6) were adults when the disease was first noted. No pertinent family history was obtained in any of them.

Cutaneous xanthomata were present in 5 of the 7 patients (Table 2; cases 1, 2, 4, 6, and 7). Only 1 of these 5 patients with cutaneous lesions (case 6) had a slight enlargement of the liver and spleen and none had attacks of abdominal pain. In all 5 patients persistent xanthomatous plaques and nodes (tuberous xanthomata) as well as eruptive papular xanthomata were present (Figures 1–3).

TABLE 2

Clinical data on own patients

NO.	NAME	SEX	FAMILY HISTORY OF XANTHOMATA	AGE AT ONSET	PRESENT AGE	FIRST SYMPTOM	TENDON XANTHOMATA			CUTANEOUS XANTHOMATA				CORONARY HEART DISEASE
							Achilles	Patellar	Fingers	Xanthelasmata eye lids	Papular xanthomata	Tuberous xanthomata	Xanthomata plana palms	
Idiopathic Hyperlipemia														
1	Valc.	M	–	32	41	Angina pec.	–	–	–	–	Bu, El, Kn	El, Fe	–	+
2	LeTo.	M	–	26	32	Pap. xanth.	–	–	+	–	Bu, He	El, Kn	+	+
3	Fole.	F	–	65	67	Milky ser.	–	–	–	–	–	–	–	+
4	Sloa.	M	–	32	34	Pap. xanth.	–	–	–	–	Bu	El, Kn	+	–
5	Ledu.	M	–	24	32	Abdom. pair	–	–	–	–	–	–	–	–
6	Leon.	M	–	8	49	Tub. xanth.	–	–	+	–	Bu, Kn	El, Ha, Fe	+	+
7	Land.	F	–	29	47	Tub. xanth.	+	+	+	–	El, Fe	El, Fe	+	–
Primary Hypercholesteremic Xanthomatosis														
8	Belz.	F	+	2	6	Tub. xanth.	+	–	+	–	–	El, Kn, Po, He	–	–
9	Ablo.	M	–	45	55	Xanthelas.	+	+	+	+	–	–	–	+
10	Sasn.	F	+	33	37	Xanthelas.	+	+	–	+	–	–	–	+
11	Tapp.	F	–	47	54	Xanthelas.	+	–	+	+	–	–	–	+
12	Giov.	M	+	11	54	Xanthelas.	+	+	–	+	–	–	–	–
13	Pear.	F	+	28	41	Xanthelas.	+	–	+	+	–	El	–	–
14	Dine.	F		19	38	Xanthelas.	+	+	+	+	–	–	–	+
15	Holm.	F		44	45	Tendon xan.	–	+	+	–	–	–	–	–
16	Klev.	F	–	51	53	Tendon xan.	–	–	–	+	–	El	+	–
17	Stil.	F	+	40	57	Xanthelas.	+	+	+	+	–	–	–	+

Explanations: Bu = Buttocks; El = Elbows; Kn = Knees; Ha = Hands; Fe = Feet; He = Heels; Po = Popliteal spaces.

The tuberous xanthomata, which measured from 0.5 to 1.5 cm. in diameter, were present in all 5 patients on the elbows, but in some also on the knees, feet and hands (see Table 2). In one patient (case 6) the tuberous xanthomata located on the hands were firm and some of them occasionally discharged gritty, calcareous material (Figure 2). Papular xanthomata were widely distributed in 1 patient (case 1), while in the other 4 they were limited to a few areas, especially the buttocks. Four patients had palmar lesions which in 3 (cases 2, 4 and 7) consisted of either flat xanthomata or yellowish discoloration of the creases, but in 1 patient (case 6) consisted of tuberous xanthomata. None of the patients had xanthelasmata of the eyelids. Tendon xanthomata were present in 3 patients in addition to the cutaneous lesions. In 2 of them (cases 2 and 6) they were limited to the extensor tendons of the fingers, while in the third patient (case 7) also the Achilles tendons, the patellar tendons and the triceps tendons near the olecranon were involved.

Of the two patients without cutaneous or tendon lesions, one patient (case 5) had severe recurrent upper abdominal pain. His case had been previously reported by Hopgood (19) in 1948. Since that time his greatly enlarged spleen had been removed and a resection of the right splanchnic nerve had been carried

FIG. 1. Idiopathic hyperlipemia (Patient 1). A, tuberous xanthomata on both elbows. B, eruptive xanthomata on one knee before low fat diet. C, same site after five months of a low fat diet. D, eruptive xanthomata on buttocks before low fat diet. E, same site after low fat diet. Most lesions have disappeared leaving hyperpigmentation at their site.

out resulting in partial relief of pain on that side. Because of his pain which now is largely confined to the left upper quadrant, this patient has had numerous admissions to the regional Veterans' Administration Hospital. In the intervals between the attacks he has felt well. Physical examination in recent years has always been without abnormal findings except for tenderness of the upper abdomen during attacks of pain.

The other patient without cutaneous lesions (case 3), began to attend the diabetic clinic at the Massachusetts General Hospital in 1941, at the age of 56. At first her diabetes was controlled by diet alone, but since 1946 protamin insulin has been administered in daily doses, up to 35 units per day. While receiving this treatment the level of the blood sugar fluctuated between 200 and 300 mg. per 100 ml. No ketones were ever noted in the urine. In 1952, when the patient was 66 years of age it was noted accidentally that she had a milky serum. It is unlikely that the hyperlipemia is related to the diabetes since the patient has been clinically well and without acidosis at all times.

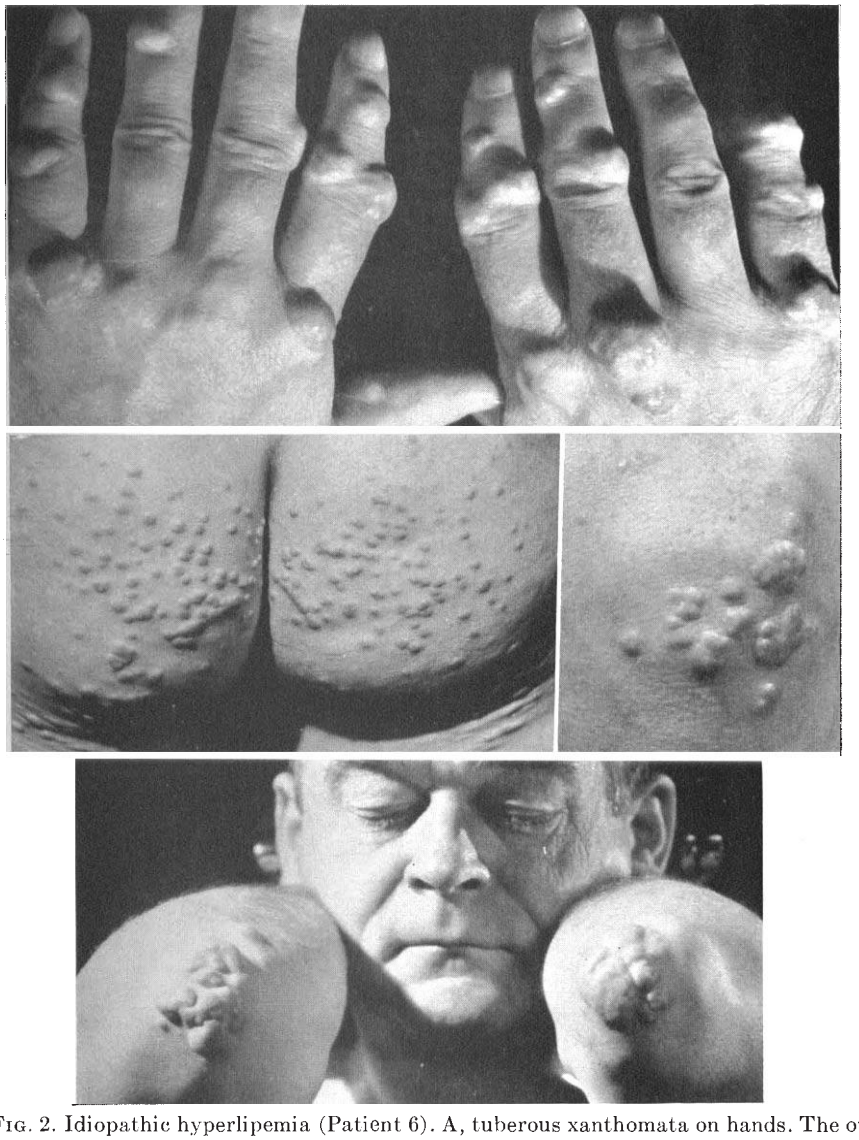

FIG. 2. Idiopathic hyperlipemia (Patient 6). A, tuberous xanthomata on hands. The outline of a tendon xanthoma can be seen just distal to the knuckle of the left middle finger. B, eruptive xanthomata on buttocks. C, eruptive xanthomata on knee. D, tuberous xanthomata on both elbows. Note the absence of eyelid xanthelasmata.

FIG. 3. Idiopathic hyperlipemia (Patient 7). Tuberous xanthomata on elbow.

Coronary heart disease was present in 4 patients. One patient (case 6) who had had xanthomata since childhood had a myocardial infarct at the age of 49; and one patient (case 3), the one with diabetes, has had attacks of angina pectoris for the past two years, since the age of 65. Coronary heart disease in these two patients could well be coincidental; but 2 patients (cases 1 and 2) have had clinical and electrocardiographic evidence of angina pectoris of moderate severity, beginning at 32 and 31 years of age, respectively.

The effect of a diet low in fat could be observed in 3 of the 7 patients (cases 1, 3 and 4). Two of them (cases 1 and 4) had tuberous as well as papular xanthomata. In both patients almost all of the papular xanthomata disappeared and the larger nodular xanthomata decreased in size (Figure 1). In addition, one patient (case 1) who had had frequent anginal attacks for the past nine years ceased to have attacks within two months of starting a diet low in fat, and had had no recurrence eight months later.

2. Primary Hypercholesteremic Xanthomatosis. Ten patients were studied (Table 2). In 2 of them (cases 8 and 12) clinical signs of the disease were already noted during childhood, while in the other 8 the disease was not diagnosed until adult life. Three of the patients (cases 13 to 15) were sisters. In addition, 4 other patients (cases 8, 10, 12 and 17) gave a family history of xanthomatous lesions, while from the remaining 3 patients no such family history was obtained.

Cutaneous lesions were present in all but 1 patient (case 15). Eight patients had xanthelasmata of the eyelids (Figure 4), but only 3 had tuberous xanthomata. In 2 of the 3 patients the tuberous xanthomata were limited to the extensor aspects of the elbows (Figure 5) and did not differ in any way from the tuberous xanthomata observed in that location in idiopathic hyperlipemia (Figures 1–3). In 1 patient, however, the six year old child, tuberous xanthomata were present also in the popliteal spaces, on the calves and overlying the Achilles tendons (Figure 6). None of the patients had eruptive papular xanthomata. Tendon xanthomata were present in all but 1 patient (case 16). They were observed on the Achilles tendons, the extensor tendons of the fingers, the patellar tendons and the triceps tendon near the olecranon (Figure 4). Whereas the xanthomata of the Achilles, patellar and triceps tendons all moved with the tendon, some of those on the extensor tendons of the fingers, especially the smaller ones, moved with the tendon sheath against the tendon. Five of the 10 patients had coronary heart disease.

B. Analysis of Plasma Lipids

Methods. Blood was obtained from each patient in the fasting state by venipuncture with a syringe containing 1.5 ml. of acid citrate dextrose solution (A.C.D.) for each 8.5 ml. of blood to be drawn. The plasma obtained by centrifugation, designated as "A.C.D. plasma" was used for all analyses except for the determination of the sedimentation rate. (The acid citrate dextrose solution contained per liter 26.7 g. trisodium citrate ($5\frac{1}{2}H_2O$), 8.0 g. citric acid monohydrate, and 22 g. dextrose.) At the same time, approximately 7 ml. of blood was drawn with a dry syringe. Two ml. were placed in a tube containing "balanced" oxalate and were used for determination of the sedimentation rate and approximately 5 ml. were placed into a tube containing a small amount of heparin powder and were used for a reference determination of nitrogen.

FIG. 4. Primary hypercholesteremic xanthomatosis (Patient 14). A, xanthelasmata of eyelids. B, xanthomata of Achilles tendons. C, tendon xanthoma just distal to the knuckle of the left middle finger. D, xanthomata of patellar tendons.

To correct to absolute values all values obtained on the plasma diluted with A.C.D., the amount of nitrogen was determined by the micro-Kjeldahl method in the A.C.D. plasma as well as in the heparinized plasma and the factor (N in heparinized plasma/N in A.C.D. plasma) was applied to all data obtained on the A.C.D. plasma.

Turbidity of the plasma was measured by the method of Geyer, Mann and Stare (35) using a Klett colorimeter for the readings. At variance with Geyer, Mann and Stare the difference between the reading for the sample and the blank was divided by 10 and expressed in units.

Total cholesterol and cholesterol esters were determined by the method of Bloor, Pelkan and Allen (36), with the photoelectric colorimeter set at 675 mμ.

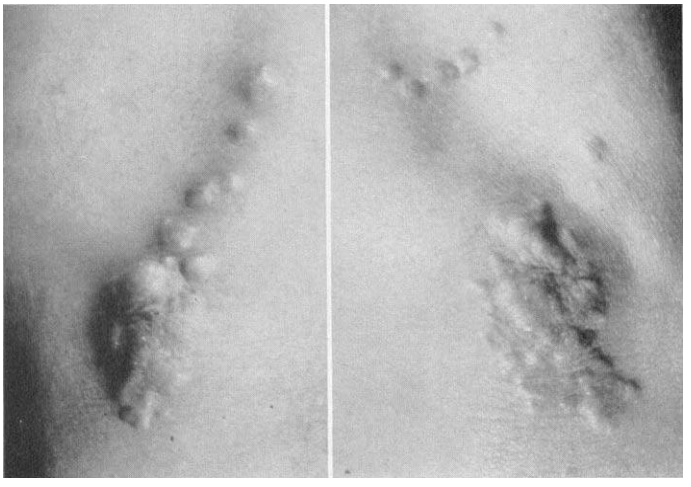

FIG. 5. Primary hypercholesteremic xanthomatosis (Patient 16). A and B, tuberous xanthomata on both elbows.

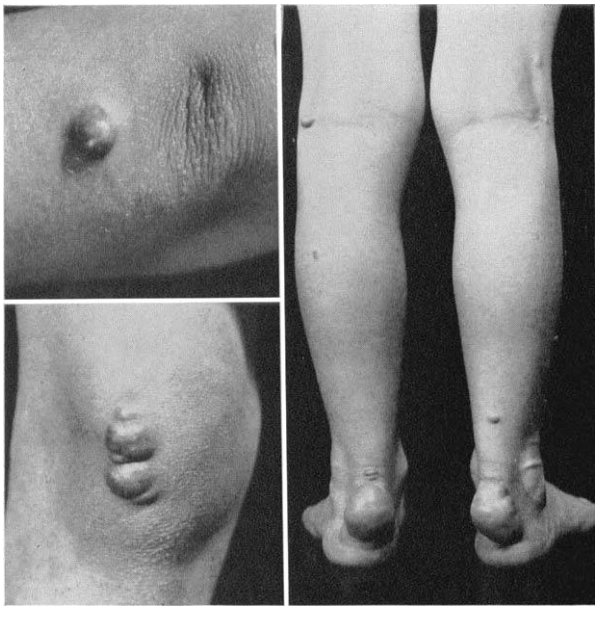

FIG. 6. Primary hypercholesteremic xanthomatosis (Patient 8). A, tuberous xanthoma on elbow. B, tuberous xanthomata on right knee. C. tuberous xanthomata overlying the Achilles tendons, on the calves and in the popliteal spaces.

Fatty acid determinations were carried out by the method of Stoddard and Drury (37).

Lipid phosphorus was determined by the method of Fiske and SubbaRow (38) following the ashing procedure of Gortner (39). Color intensity was measured at 700 mμ. The factor 25.0 was used to convert lipid phosphorus to phospholipid.

Neutral fat was calculated, according to Peters and Man (40), as follows: From the total fatty acids expressed in milliequivalents per liter was subtracted the sum of the fatty acids

combined as cholesterol ester and phospholipids. The remainder was assumed to represent fatty acids combined as neutral fat. This value was converted into milligrams per 100 ml. by multiplying it by 28.3.

Total lipids were calculated by adding first the amounts in mg. of neutral fat, of phospholipids and of free cholesterol and then adding the amount in mg. of esterified cholesterol multiplied by 1.69. (The factor of 1.69 was used to convert esterified cholesterol into cholesterol esters. The weight of esterified cholesterol is only that of the cholesterol; the weight of cholesterol esters includes that of the esterified fatty acids.)

Sedimentation rate determinations were carried out according to the method of Wintrobe and Landsberg (41). The values obtained were corrected to apply to a hematocrit value of 45 per cent.

1. Idiopathic Hyperlipemia. The plasma of all 7 patients revealed a moderate to considerable elevation of the cholesterol and phospholipids and a very considerable elevation of the fatty acids and, by calculation, of the neutral fat (Table 3). The values for cholesterol varied from 384 to 1,000 mg. per 100 ml. of plasma, averaging 614 mg. (normal range from 160 to 290 mg.). The values for phospholipids varied from 338 to 1,110 mg. per 100 ml., averaging 575 mg. (normal range from 160 to 310 mg.); and the values for fatty acids varied from 1,456 to 6,470 mg. per 100 ml., averaging 2,696 mg. (normal range from 190 to 450 mg.). Calculation of the values for neutral fat resulted in values ranging from 994 to 5,850 mg., averaging 2,116 mg. (normal range from 0 to 400 mg.). The ratio of cholesterol ester to total cholesterol was within the normal range, with values from 51 to 65 per cent, averaging 58 per cent (normal range from 50 to 70 per cent).

Measurement of the turbidity gave values ranging from 12.9 to 116.0 units and averaging 26.3 units (normal range of from 1 to 5 units). It was observed that at turbidity readings below 5 units the plasma appeared clear; at values between 5 and 10 opalescent; at values between 10 and 45 milky; and at values higher than 45 like thick cream. In an attempt to establish some relationship between the degree of turbidity and the amounts or proportions of the various lipids in the plasma the degree of turbidity was plotted against the concentration of the various lipids. No relationship was observed between the degree of turbidity and the absolute amounts of either cholesterol or phospholipids, but some relationship existed between the degree of turbidity and the amount of neutral fat (Figure 7). Also, to a certain degree, an inverse relationship was noted between the degree of turbidity and the percentage of phospholipids in the total lipids (Figure 8).

The amount of nitrogen in the plasma was increased above normal in several patients. If the amount of nitrogen is multiplied by 6.25 and expressed as total protein, as it is customarily done in medical writing, the values varied from 6.63 to 9.25 gm. per 100 ml. of plasma, averaging 7.86 gm. (normal range from 6.8 to 7.8 gm.). The values for total protein exceeded 8.0 gm. per 100 ml. in 5 of the 7 patients.

The erythrocyte sedimentation rate, determined in 6 patients, was normal in 1, moderately elevated in 2, and considerably elevated in 3. While normally the corrected sedimentation rate varies from 0.1 to 0.4 mm. per minute, it averaged

TABLE 3

Values of nitrogen and lipids, degree of turbidity and sedimentation rate in the plasma of patients with idiopathic hyperlipemia

PATIENT	DATE	TOTAL PROTEIN		SEDIMENTATION RATE	TURBIDITY	TOTAL FATTY ACIDS	NEUTRAL FAT	CHOLESTEROL				PHOSPHOLIPIDS
		N	N × 6.25					Total	Free	Esterified		
		gm./100 ml.		mm./hr.	units	mg./100 ml		mg./100 ml			%	mg./100 ml.
Normal range												
low		1.09	6.80	0.1	1.9	190	0	160	50	120	50	160
high		1.25	7.80	0.4	4.5	450	400	290	100	220	70	310
Normal average		1.17	7.30	0.2	2.6	300	180	208	63	146	60	240
1	4/24/52	1.48	9.25	0.8	31.7	4040	3005	1000	463	537	54	1110
*	9/30/52	—	—	—	8.4	1690	1210	340	140	200	60	560
*	10/20/52	1.36	8.50	—	15.7	1930	1480	386	177	209	54	526
*	1/27/53	1.47	9.19	1.6	9.4	2501	1840	511	233	288	56	770
2	11/12/52	1.20	7.50	—	49.7	2920	2270	730	255	475	65	563
3	5/19/52	1.26	7.88	1.5	15.0	2340	1850	384	186	198	52	614
*	12/9/52	1.23	7.69	—	5.3	1530	1140	345	130	215	62	408
*	2/13/53	1.20	7.50	1.0	5.7	1721	1495	311	146	165	53	407
4	7/23/51	1.09	6.81	0.3	—	—	—	510	—	—	—	338
	11/27/51	—	—	—	—	1740	—	760	—	—	—	510
	3/24/52	1.19	7.44	0.4	20.0	1990	—	905	—	—	—	580
*	10/14/52	1.29	8.06	—	10.1	1610	940	667	251	416	62	607
5	10/25/51	1.32	8.25	1.7	38.7	4760	—	555	—	—	—	471
	6/24/52	1.24	7.75	—	96.6	5240	4750	540	265	275	51	600
	10/29/52	1.34	8.38	—	116.0	6470	5850	752	295	457	61	667
	2/10/53	1.24	7.75	—	89.4	4453	4100	484	206	278	57	424
6	11/26/51	1.10	6.88	—	16.1	1456	—	495	—	—	—	406
	9/24/52	1.06	6.63	0.4	20.0	1570	994	575	217	358	62	532
	4/21/53	1.48	9.25	0.6	19.0	2156	1636	494	219	275	56	519
7	4/15/52	1.35	8.44	1.3	12.9	1618	1000	622	—	—	—	523
Average†		1.26	7.86	1.0	26.3	2696	2116	614	273	377	58	575

* Determination carried out while the patient had a diet low in fat.

† For the calculation of the average the first value obtained in each patient was taken.

in the 6 patients 1.0 mm. per minute and measured in the four patients with the greatest elevation 1.3, 1.5, 1.6 and 1.7 mm. per minute, respectively.

The effect of a low fat diet on the plasma lipids could be studied in 3 patients. Although none of the patients adhered to the diet strictly, a considerable decrease in turbidity was noted in all: namely from 31.7 to 8.4 units; from 15.0 to 5.3 units; and from 20.0 to 10.1 units, respectively. Two patients (cases 1 and 3)

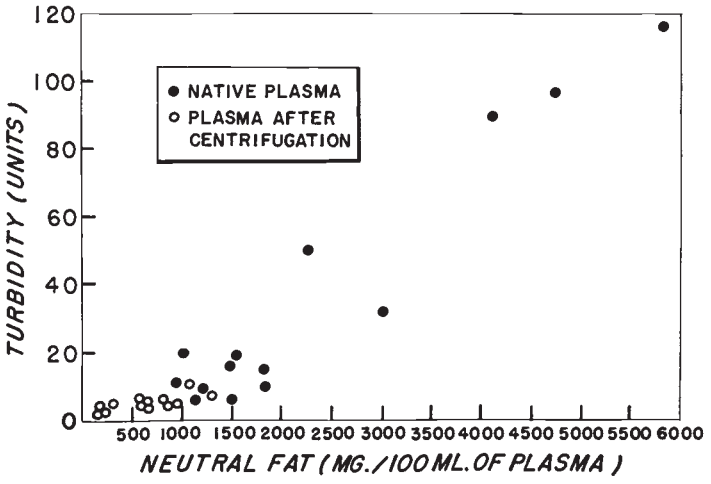

FIG. 7. Idiopathic hyperlipemia. A general but not a linear, predictable relationship exists between the degree of turbidity and the amount of neutral fat in the plasma.

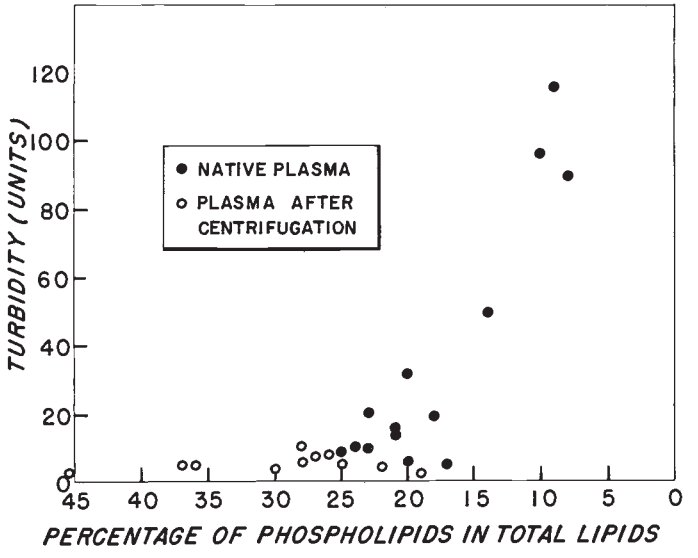

FIG. 8. Idiopathic hyperlipemia. A general, inverse relationship exists between the degree of turbidity and the percentage of phospholipids in the total lipids in the plasma.

showed a considerable decrease and one patient (case 4) a moderate decrease in fatty acids. Furthermore, the amount of cholesterol decreased in all 3 patients, while the phospholipids decreased in 2 patients (cases 1 and 3) (see Table 3).

2. Primary Hypercholesteremic Xanthomatosis. The amounts of cholesterol and phospholipids were increased in all 10 patients; but with the exception of 1 patient (case 8), the only child in this series, the increase was moderate, the values for cholesterol not exceeding 528 mg. per 100 ml. of plasma; and for phospholipids not exceeding 445 mg. (Table 4). The average for cholesterol in all 10 patients

TABLE 4

Values of nitrogen and lipids, degree of turbidity and sedimentation rate in the plasma of patients with primary hypercholesteremic xanthomatosis

PATIENT	DATE	TOTAL PROTEIN		SEDIMENTATION RATE	TURBIDITY	TOTAL FATTY ACIDS	NEUTRAL FAT	CHOLESTEROL				PHOSPHOLIPIDS
		N	N × 6.25					Total	Free	Esterified		
		gm./100 ml.		mm./hr.	units	mg./100 ml.		mg./100 ml.			%	mg./100 ml.
Normal range												
low		1.09	6.80	0.1	1.9	190	0	160	50	120	50	160
high		1.25	7.80	0.4	4.5	450	400	290	100	220	70	310
Normal average		1.17	7.30	0.2	2.6	300	180	208	63	146	60	240
8	10/9/51	1.31	8.19	—	4.8	1104	—	902	—	—	—	642
	4/7/52	1.23	7.69	0.8	4.5	1034	—	897	—	—	—	515
	3/11/53	1.50	9.38	0.6	2.8	968	108	961	283	678	71	582
9	1/21/52	1.24	7.75	1.5	3.2	474	—	333	—	—	—	292
	7/7/52	1.20	7.50	—	2.6	492	210	280	125	155	55	275
10	3/3/52	1.21	7.56	0.6	5.2	—	—	471	—	—	—	398
	11/12/52	—	—	—	—	452	108	305	110	195	64	320
11	5/6/52	1.34	8.38	1.6	3.3	550	133	528	264	264	50	360
	11/24/52	—	—	—	—	452	108	305	110	195	64	320
12	6/18/52	1.16	7.25	0.9	2.8	660	252	403	186	217	54	399
	12/2/52	1.18	7.38	—	—	490	54	405	165	240	59	413
	4/7/53	1.23	7.69	0.8	3.5	602	219	389	192	197	51	386
13	7/16/52	1.28	8.00	1.3	2.0	493	144	427	234	193	45	331
	3/13/53	1.20	7.50	0.4	2.6	733	372	480	216	264	55	280
14	7/16/52	1.36	8.50	1.5	2.0	572	136	489	232	257	53	397
	3/11/53	1.18	7.38	0.4	2.7	711	190	500	164	336	67	445
15	7/16/52	1.22	7.63	—	2.8	550	139	400	140	260	65	358
	3/11/53	1.18	7.38	0.6	3.2	479	94	425	165	260	61	313
16	9/12/52	1.34	8.38	1.7	4.0	796	314	520	200	320	62	367
	5/4/53	1.32	8.25	—	3.9	581	264	381	181	200	52	273
17	12/29/52	1.29	8.06	1.4	2.9	550	68	477	167	310	65	411
	4/7/53	1.30	8.13	1.6	3.7	667	213	477	213	264	55	393
Average†		1.28	7.97	1.2	3.3	620	161	495	194	285	58	396

† For the calculation of the average the first value obtained in each patient was taken.

was 495 mg. per 100 ml. of plasma (normal range from 160 to 290 mg.). For phospholipids the average in the 10 patients was 396 mg. (normal range from 160 to 310 mg.). The amount of fatty acids was elevated but slightly, exceeding a value of 800 mg. per 100 ml. only in the child, in whom the amount was 1,104 mg. The average value for fatty acids in all 10 patients was 620 mg. (normal range from 190 to 450 mg.). The entire increase in fatty acids could be accounted for by the increase in those fatty acids that were associated with the cholesterol and phospholipids. Calculation of the amount of neutral fat resulted in values from 54 to 372 mg. per 100 ml. averaging 161 mg. Thus, all values fell within the normal range which extends from 0 to 400 mg. per 100 ml. of plasma. The proportion of esterified cholesterol in total cholesterol was normal, with values ranging from 45 to 71 per cent and averaging 58 per cent (normal range from 50 to 70 per cent).

The plasma of all patients was entirely clear and measurement of the turbidity resulted in values ranging from 2.0 to 5.2 units, averaging 3.3 units (normal range from 1 to 5 units).

The amount of total protein (obtained by multiplying the value for nitrogen by 6.25) varied from 7.25 to 9.38 gm. per 100 ml., averaging 7.97 gm. In 6 of the 10 patients values of 8 gm. or higher were obtained.

The erythrocyte sedimentation rate was elevated in all 10 patients, varying from 0.4 to 1.7 mm. per minute, and averaging 1.2 mm.

DISCUSSION

Clinical Appearance. Comparison of the clinical manifestations in our 7 patients with idiopathic hyperlipemia with those in our 10 patients with primary hypercholesteremic xanthomatosis reveals greater similarities between these two diseases than perusal of the literature suggests: Tuberous xanthomata, tendon xanthomata and coronary heart disease, so far not described in idiopathic hyperlipemia and regarded as characteristic of primary hypercholesteremic xanthomatosis, were observed in both diseases. While in the 18 cases of idiopathic hyperlipemia with cutaneous lesions reported in the literature eruptive papular xanthomata were the only cutaneous manifestation, all 5 of our cases of idiopathic hyperlipemia with cutaneous lesions had, in addition, large persistent xanthomata, indistinguishable from the tuberous xanthomata of primary hypercholesteremic xanthomatosis. They were present in all 5 patients on the elbows and, in some instances, also on the knees, hands and feet. Furthermore, xanthomata of the tendons, although less frequent and less conspicuous than in primary hypercholesteremic xanthomatosis, were present in 3 of the 7 patients with idiopathic hyperlipemia. They were limited to the extensor tendons of the fingers in 2 patients, but were present also on the Achilles, patellar and olecranon tendons in 1 patient. In this patient who also had tuberous xanthomata (Figure 3), our diagnosis at first had been primary hypercholesteremic xanthomatosis rather than idiopathic hyperlipemia and her case was erroneously reported as one of primary hypercholesteremic xanthomatosis in a previous paper (42). Finally, 4 of our patients with idiopathic hyperlipemia had coronary heart dis-

ease which in 2 patients had begun early in life, namely at thirty-one and thirty-two years of age, respectively. Of interest is also that attacks of upper abdominal pain, presumably due to pancreatitis, occurred in only 1 of our 7 patients with idiopathic hyperlipemia, whereas they had been observed in 23 of the 41 cases reported in the literature.

Among our 10 patients with primary hypercholesteremic xanthomatosis, 8 had xanthelasmata of the eyelids. The frequent occurrence of this lesion in primary hypercholesteremic xanthomatosis is noteworthy since so far it has never been observed in patients with idiopathic hyperlipemia. Furthermore, tendon xanthomata were common and extensive in the patients with primary hypercholesteremic xanthomatosis being present in 9 of the 10 patients. However, tuberous xanthomata were noted in only 3 of our patients with primary hypercholesteremic xanthomatosis as compared to 5 of our patients with idiopathic hyperlipemia.

It thus appears that xanthelasmata of the eyelids are the only clinical sign occurring in primary hypercholesteremia xanthomatosis but not in idiopathic hyperlipemia; while papular xanthomata, especially on the buttocks, hepatosplenomegaly and abdominal cramps are clinical indications of idiopathic hyperlipemia. Tendon xanthomata on the Achilles, patellar and olecranon tendons are common findings in primary hypercholesteremic xanthomatosis, although in rare instances they may be observed also in idiopathic hyperlipemia. However, tuberous xanthomata, xanthomata of the extensor tendons of the fingers and coronary heart disease occur quite frequently in both diseases.

Chemical Findings. The amounts of cholesterol and phospholipids were elevated in both diseases, although on the average, to a higher degree in idiopathic hyperlipemia than in primary hypercholesteremic xanthomatosis. In both diseases the free and the esterified cholesterol were elevated to an equal degree and thus the percentage of esterified cholesterol in total cholesterol was within the normal range in both diseases. The significant difference between the two diseases lay in the amount of neutral fat present in the plasma. While the amount of neutral fat was normal in the patients with primary hypercholesteremic xanthomatosis, it was greatly increased in those with idiopathic hyperlipemia. The average amount of neutral fat in the patients with primary hypercholesteremic xanthomatosis was 161 mg. per 100 ml., and in the patients with idiopathic hyperlipemia 2,116 mg., thirteen times higher.

The turbid appearance of the plasma in idiopathic hyperlipemia, in our opinion, is caused by the presence of excessive quantities of neutral fat in the plasma. Cholesterol and phospholipids, even if they are present in large amounts, as in some patients with primary hypercholesteremic xanthomatosis, do not cause turbidity. This is due to the fact that the cholesterol and the phospholipids are closely united with proteins to lipoprotein molecules too small in size to scatter light appreciably (43). It is true that some lipoprotein molecules, as Gofman (44) has shown, contain a certain amount of neutral fat. However, when neutral fat is present in the plasma in large amounts, as it is in idiopathic as well as in secondary hyperlipemia, it occurs predominantly in large aggregates (chylomicra) (45). Chylomicra, due to their large size, scatter sufficient light to produce visible

turbidity of the serum. That only an approximate but no linear, predictable relationship exists between the degree of turbidity and the amount of neutral fat as evident from Figure 7, may be due to the fact that the degree of turbidity depends not alone on the amount of neutral fat but also on the size of the chylomicra which may vary in different cases. (More about the physical state of the lipids and lipoproteins in the plasma will be said in Part II of this paper.)

Ahrens and Kunkel (46) have proposed the theory that in high lipid sera clarity was closely correlated with elevated proportions of serum phospholipids; and turbidity with low proportions of phospholipids. They believe that the phospholipids act as natural emulsifying agents to hold the other lipids in a clear solution. One may perhaps conclude from their data that the phospholipids can reduce turbidity to a limited degree. Nevertheless, we believe that the somewhat inverse relationship between the degree of turbidity and the proportion of phospholipids in the total lipids, as observed in the plasma of idiopathic hyperlipemia (see Figure 8), exists only because, with the great increase in the amount of neutral fat, the relative amount of phospholipids in the plasma naturally decreases. The absolute amounts of phospholipids are, on the average, greater in the turbid plasmas of idiopathic hyperlipemia than in the clear plasmas of primary hypercholesteremic xanthomatosis and the cholesterol-phospholipids ratios are similar in both diseases.

The sedimentation rate was increased in all 10 patients with primary hypercholesteremic xanthomatosis and in 5 of 6 patients with idiopathic hyperlipemia. Such increase has occasionally been noted (cases 3, 4, 5, 11, 17, 18, 21a & b, 22a, b, d) (See Table 1). Little is known about the factors causing variations in the sedimentation rate. Specific gravity and viscosity of the plasma have no appreciable effect on it, whereas rouleaux formation of the red cells increases it (27). It is possible, therefore, that the abnormally high amounts of lipids and lipoproteins in the plasma increase rouleaux formation of the red cells and thus cause an increase in the sedimentation rate.

SUMMARY

1. Clinical examination of 7 patients with idiopathic hyperlipemia revealed that, although not previously reported, tuberous xanthomata, tendon xanthomata and coronary heart disease may occur in that disease.

2. Comparison of the clinical features in our 7 patients with idiopathic hyperlipemia with those in 10 patients with primary hypercholesteremic xanthomatosis revealed that xanthelasmata of the eyelids occur only in primary hypercholesteremic xanthomatosis, whereas papular xanthomata, hepatosplenomegaly and abdominal cramps, probably due to pancreatitis, are observed only in idiopathic hyperlipemia. Tendon xanthomata on the Achilles, patellar and olecranon tendons are common in primary familial xanthomatosis and rare in idiopathic hyperlipemia. On the other hand, xanthomata of the extensor tendons of the fingers, tuberous xanthomata and coronary heart disease occur quite frequently in both diseases.

3. In both diseases the values for cholesterol and phospholipids are increased;

but only idiopathic hyperlipemia is accompanied by an increase in neutral fat. The high concentration of neutral fat is regarded as the sole cause for the turbidity of the plasma in idiopathic hyperlipemia. In both diseases the erythrocyte sedimentation rate is increased, probably due to an effect of the lipids and lipoproteins on the rouleaux formation of the red cells.

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